migraine, and other episodic neurological disorders, such as epilepsy, have been mapped to chromosome 19p13. A brain-specific P/Q type calcium channel subunit gene, covering 300 kb with 47 exons is provided. The exons and their surroundings reveal polymorphic variations and deleterious mutations that are linked to various types of cation channel dysfunctions causing episodic neurological disorders in man or animals.--

REMARKS

New claims 38-40 have been added. Support for these claims is found for example on page 3, lines 3-16, page 4, lines 4-22, page 17, lines 12-16, page 18 line 33 through page 22, line 3. The amendments to claims 34 and 37 find support for example on page 5, lines 4-8 and page page 5, line 27 through page 6, line 2. The remaining amendments are to put the claims in standard US format. No new matter is added by the amendments and the Examiner is respectfully requested to enter them.

CONCLUSION

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (650) 328-4400.

Respectfully submitted,

Dated: July 14, 2003

Barbara Rae-Venter, Ph.D.
Reg. No. 32,750

Rae-Venter Law Group, P.C.
PO Box 1898
Monterey, CA 93942-1898
Phone: (831) 648-3090
Facsimile: (831) 242-0137

BRV/mnb

PATENT **ATTORNEY DOCKET NO. VEOC.003.02US**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Frants *et al.*

Serial No.: Not Yet Assigned

Filed: July 14, 2003

Title: A gene related to migraine in man

MARKED UP COPY OF CLAIMS

Mail Stop PATENT APPLICATION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The Examiner is respectfully requested to make the amendments shown below. A Clean Copy of the text of the claims following entry of the amendments is attached hereto.

IN THE CLAIMS:

1. (Amended) An isolated [and/or recombinant] nucleic acid encoding [a Ca^{2+}-channel] an α1 subunit of a P/Q-type gated calcium channel [related to (familial hemiplegic) migraine and/or episodic ataxia type-2 derived from, related to or associated with a gene which in humans is

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Matthew Bogner
(Signature)

Matthew Bogner
(Printed Name)

present on chromosome 19p13.1-19p13.2] or a specific fragment or homolog or derivative [thereof] of said calcium channel.

2. (Amended) [A] The nucleic acid according to claim 1, wherein said nucleic acid [which] is a cDNA [molecule].

3. (Amended) [A] The cDNA [molecule] according to claim 2, wherein said cDNA [comprising] comprises a [6800] 6789 bp coding region.

4. (Amended) [A] The nucleic acid according to claim 1, [2 or 3 which], wherein said cDNA is of human origin.

5. (amended) [A] The nucleic acid according to claim 4, wherein the nucleotide sequence of said nucleic acid [and showing] has at least 70% homology with the [nucleic acid] nucleotide sequence [as listed in figure 1] depicted in SEQ ID NO: 1-42.

6. (Amended) [A] The nucleic acid according to [any of claims 1-5] claim 1, wherein the nucleotide sequence of said nucleic acid [and showing] has at least 90% homology with the [nucleic acid] nucleotide sequence [as listed in figure 1] depicted in SEQ ID NO: 1-42.

7. (Amended) [A] The nucleic acid according to [any of claims 1-6 and showing a] claim 38, wherein said one or more mutation [at codon 192 resulting in the] is at a codon in said nucleic acid which results in an amino acid change in said calcium channel respectively selected from the group consisting of codon 192: replacement of arginine by glutamine; codon 666: a replacement of threonine by methionine; codon 714, a replacement of valine by alanine; and codon 1811: a replacement of isoleucine by leucine.

8. (Amended) [A] An isolated nucleic acid according to [any of claims 1-7 and showing] Claim 1, wherein said nucleic acid comprises a mutation at codon 666 resulting in the replacement of threonine by methionine.

9. (Amended) [A] An isolated nucleic acid according to [any of claims 1-8 and showing] Claim 1, wherein said nucleic acid comprises a mutation at codon 714 resulting in the replacement of valine by alanine.

10. (Amended) [A] An isolated nucleic acid according to [any of claims 1-9 and showing] Claim 1, wherein said nucleic acid comprises a mutation at codon 1811 resulting in the replacement of isoleucine by leucine.

11. (Amended) [A] The isolated nucleic acid according to [any of claims 1-10 and] claim 1, wherein said nucleic acid [comprising] comprises a CA-repeat sequence [as shown in figure 2].

12. (Amended) [A] The isolated nucleic acid according to [any of claims 1-11 and comprising] claim 1, wherein said nucleic acid comprises a (CAG)n repeat sequence as shown in [figure] table 2.

13. (Amended) [A] The isolated nucleic acid according to [any of claims 1-12 and comprising] claim 1, wherein the coding sequence of said nucleic acid comprises a polymorphism [in the coding sequence].

14. (Amended) [A] The isolated nucleic acid according to claim 13 [and comprising a], wherein said polymorphism [in the coding sequence as] comprises a nucleotide change shown in table 2.

15. (Amended) [A] The isolated nucleic acid according to claim 13 or 14, wherein said

nucleic acid [and comprising] comprises a mutation at codon 454 resulting in a replacement of alanine by threonine in said calcium channel.

16. (Amended) [A] The isolated nucleic acid according to [any of claims 1-15] claim 1, wherein said nucleic acid [and comprising] comprises a deletion.

17. (Amended) [A] The isolated nucleic acid according to [any of claims 1-16] claim 1, wherein said nucleic acid [and comprising] comprises a frameshift at codon 1266.

18. (Amended) [A] The isolated nucleic acid according to [any of claims 1-17] claim 1, wherein said nucleic acid [and comprising] comprises a mutation [resulting] which results in [abberant] aberrant splicing.

19. (Amended) [A] The isolated nucleic acid according to [any of claims 1-18] claim 18, wherein said [and comprising a mutation resulting in] [abberant] aberrant splicing is of intron 28.

20. (Amended) An isolated [and/or recombinant] nucleic acid encoding a [CA^{2+}] calcium channel subunit or a functional fragment thereof, wherein said nucleic acid is obtained from a mammal [related to (familial hemiplegic)] diagnosed as having one or both of familial hemiplegic migraine [and/or] and episodic ataxia type 2.

21. (Amended) [An] The isolated [and/or recombinant] nucleic acid [encoding a CA^{2+}] according to claim 20, wherein said calcium channel subunit is a β2 subunit [related to (familial hemiplegic) migraine and/or episodic ataxia type 2], wherein said nucleic acid is derived from, related to or associated with a gene which in humans is present on chromosome 10p12 [or a specific fragment thereof].

22. (Amended) A method for [localising or] identifying a gene which encodes a P/Q-type

gated calcium channel, said method comprising:

contacting genetic material with a [using] a nucleic acid molecule or a fragment of fragments thereof according to [any of claims 1-21] claim 1 or claim 20.

23. (Amended) [A] The method according to claim 22 wherein [the] said gene is related to an episodic neurological [disorders] disorder.

24. (Amended) [A] The method according to claim 22 [or 23], wherein [the] said gene is related to migraine.

25. (Amended) [A] The method according to claim 22, [23 or 24] wherein [the] said gene is related to one or more neurological disorder selected from the group consisting of FHM, [and/or] EA-2, [and/or] and autosomal dominant cerebellar ataxia.

26. (Amended) A method of distinguishing between alleles of a gene which encodes a P/Q-type gated calcium channel, said method comprising:

[using] contacting said gene with a nucleic acid molecule or a fragment of fragments thereof according to [any of claims 1-21] claim 20.

27. (Amended) [A] The method according to [any of claims 23-26 in which the] claim 23 or claim 26, wherein said gene is of human origin.

28. (Amended) [A] The method according to [any of claims 23-27 which comprises selecting] claim 23 or claim 26, wherein said gene is identified in a cell or an animal.

29. (Amended) A recombinant expression vector comprising a nucleic acid molecule [or a fragment of fragments thereof] according to [any of claims 1-21] claim 1.

30. (Reiterated) A cell or an animal comprising a vector according to claim 29.

31. (Amended) A transgenic non-human cell, an isolated transgenic cell or [an] a non-human transgenic animal comprising a nucleic acid molecule [or a fragment of fragments thereof] according to [any of claims 1-21] claim 1.

32. (Amended) A non-human cell, an isolated cell or [an] a non-human animal comprising a gene which encodes a P/Q-type gated calcium channel [selected] identified by [a] the method according to claim 28.

33. (Amended) A non-human cell, an isolated cell or [an] a non-human animal comprising a genome in which a nucleic acid [sequences] corresponding to said nucleic acid [molecules] according to [any of claims 1-21 have] claim 1 has been modified.

34. (Amended) [Use of a cell or an animal according to any of claim 30-33 to test or develop specific medication for the treatment of] A method for screening for an agent useful for treating FHM, EA-2, SCA6, migraine or other neurological [disorders] disorder associated with cation channel dysfunction, said method comprising:

comparing phenotypic characteristics relating to cation channel dysfunction of a first animal contacted with said agent with those of a second animal not contacted with said agent, wherein the genome of said first animal and said second animal comprise a nucleic acid encoding dysfunctional $\alpha 1$ subunit of a P/Q-type gated calcium channel, whereby an agent useful for treating FHM, EA-2, SCA6, migraine or other neurological disorder is identified by a decrease in phenotypic characteristics relating to calcium channel dysfunction in said first transgenic mouse in comparison to said second transgenic mouse.

35. (Amended) A protein or peptide comprising an amino acid sequence encoded by a nucleic acid molecule[, or a fragment or fragments thereof, according to any of claims 1-21] according to

claim 1.

36. (Reiterated) A natural or synthetic antibody directed against a protein or peptide according to claim 35.

37. (Amended) [Use of a protein or peptide or antibody according to claim 35 or 36 to detect or diagnose] A method for diagnosing FHM, EA-2, SCA6, migraine or other neurological disorders associated with cation channel dysfunction, said method comprising:

detecting a protein or a peptide encoded by the nucleic acid according to claim 38 in a patient.

Add the following new claims.

--38. (New) The nucleic acid according to Claim 1, wherein said nucleic acid comprises one or more mutation which results in dysfunction of said calcium channel.

39. (New) A non-human animal with phenotypic characteristics relating to calcium channel dysfunction, the genome of which comprises:

a nucleic acid encoding dysfunctional $\alpha 1$ subunit of a P/Q-type gated calcium channel.

40. (New) The non-human animal according to claim 39, wherein said non-human animal is a mouse.--.

Respectfully submitted,

Dated: July 14, 2003

Barbara Rae-Venter, Ph.D.
Reg. No. 32,750

Rae-Venter Law Group, P.C.
PO Box 1898
Monterey, CA 93942-1898
Phone: (831) 648-3090
Facsimile: (831) 242-0137

BRV/mnb